Citation:

Pomeranz A, Dolfin T, Korzets Z, Eliakim A, Wolach B. Increased sodium concentrations in drinking water increase blood pressure in neonates. *J Hypertens.* 2002; 20: 203–207.

PubMed ID: 11821704

Study Design:

Randomized controlled trial with crossover

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

⊙ NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To evaluate changes in blood pressure during the first two months of life in neonates receiving low-sodium mineral water (LSMW), high-sodium tap water (HSTW) or breast milk.

Inclusion Criteria:

- Newborn infants enrolled in the Meir General Hospital's (in Israel) neonatal unit
- Jewish infants
- Infants from families with no history of hypertension.

Exclusion Criteria:

- Infants not born in Meir General Hospital (in Israel) and not enrolled in the hospital's neonatal unit
- Infants from families with a history of hypertension.

Description of Study Protocol:

Recruitment

58 newborn infants enrolled in the Meir General Hospital's (in Israel) neonatal unit were randomly assigned to two study groups, as described below.

Design

- In this randomized prospective study, randomization was accomplished by allocating infants whose mothers refused to breastfeed and who met the inclusion/exclusion criteria to one of the two study groups:
  - Group 1 (N=25): Fed with a formula diluted with low-sodium mineral water (LSMW)

- Group 2 (N=33): Fed with the same formula diluted with high-sodium tap water (HSTW)
- The control group (Group 3) was composed of breastfed infants.
- Weekly weight, height, head circumference, heart rate, systolic (SBP) and diastolic (DBP) blood pressure and mean (MAP) arterial pressures were recorded during the first eight weeks. Urinary sodium:creatinine ratio was determined monthly during the initial two months of study. At completion of eight weeks, group 1 infants reverted to a diet similar to that of group 2. At week 24 (six months of age), a follow-up blood pressure measurement was performed in 11, 20 and seven infants in groups 1, 2 and 3, respectively.

Dietary Intake/Dietary Assessment Methodology

- The experimental groups were fed formula diluted as follows:
  - Group 1 infants were fed a formula diluted with LSMW (Eden Spring Mineral Water) with a sodium concentration of 32 mg per L (1.4 mmol per L) up until eight weeks of age when they reverted to a diet similar to group 2 (high sodium intake)
  - Group 2 infants were fed a formula diluted with HSTW with a sodium concentration of 196 mg per L (8.5 mmol per L)
  - Group 3 infants were fed breastmilk only.
- Dietary Assessment methodology in terms of how data on dietary intake of Group 1 and Group 2 formulas and breastmilk was collected.

Intervention

- The intervention involved feeding formula diluted with water containing either low-sodium mineral water (LSMW) or high-sodium tap water (HSTW) to two different groups of neonates for eight weeks (with a group of breastfed infants serving as a control), and then having the group consuming the low-sodium formula revert after eight weeks to consuming the high-sodium formula
- On a weekly basis, weight, height, head circumference, heart rate, SBP and DBP and MAP were recorded during the first eight weeks. At week 24 (six months of age), a follow-up blood pressure measurement was performed in 11, 20 and seven infants in groups 1, 2 and 3, respectively.

Statistical Analysis

- Differences in group means analyzed by analysis of variance followed by Newman-Keuls mutiple comparisons of Student's T-test for independent samples
- Stepwise multiple regression analysis was used to test correlation between urinary sodium:creatinine ratio and blood pressure
- Significant differences were denoted by $P<0.05$.

Data Collection Summary:

Timing of Measurements

- Weekly weight, height, head circumference, heart rate, SBP, DBP and MAP were recorded during the first eight weeks
- Urinary sodium:creatinine ratio was determined monthly during initial two months of study
- At week 24 (six months of age), a follow-up blood pressure measurement was performed in the experimental and control groups.

Dependent Variables

- *Variable 1:* Blood pressure-SBP, DBP and MAP (measured using Dinamap 8100 Vital Signs Monitor using Doppler technique; blood pressure was recorded at infant's home during sleep after feeding, with appropriately sized cuff on tight upper extremity, overlying the brachial artery)
- *Variable 2:* Weight
- *Variable 3:* Height
- *Variable 4:* Urinary sodium:creatinine ratio.

Independent Variables

- Intake of formula diluted with low-sodium mineral water (LSMW) (sodium concentration of 218mg per L (9.5mmol per L)
- Intake of formula diluted with high-sodium tap water (HSTW) (sodium concentration of 382mg per L (16.6mmol per L)
- Intake of breast milk [sodium content of 161mg per L (7.0mmol per L)].

Sodium concentrations of formula and breast milk determined by flame photometer.

Description of Actual Data Sample:

- *Initial N:* 58 infants
- *Attrition (final N):* Initial analysis on 58 infants, final analysis on 38 infants
    - Followed through eight weeks:
        - Group 1 experimental infants, N=25
        - Group 2 experimental infants, N=33
        - Group 3 control infants, N=15
    - Followed through 24 weeks (six months):
    - Group 1 experimental infants, N=11
    - Group 2 experimental infants, N=20
    - Group 3 control infants, N=7
- *Age:* Newborn infants followed through six months of age
- *Ethnicity:* Jewish infants
- *Other relevant demographics:* Experimental and control groups were well matched regarding gestational age and Apgar scores
- *Anthropometrics:* Experimental and control groups were well matched regarding body weight, height and head circumference
- *Location:* Israel.

Summary of Results:

Key Findings

- In comparison with the LSMW-low-sodium intake group and breastfed infants, the HSTW-high-sodium intake group exhibited a progressive increase in MAP, SBP and DBP from week four that attained significance at weeks six to eight of study period (P<0.05)
- From the sixth week, SBP, DBP and MAP were found to be significantly greater in group 2 (HSTW-high-sodium intake) than in groups 1 (LSMW-low-sodium intake) and three

(breastfed-lowest sodium intake) (P<0.05)

- In crossover, when group 1 infants reverted to a high-salt intake after eight weeks, their blood pressure values increased towards those observed in group 2 (HSTW-high-sodium intake)
- Urinary sodium:creatinine ratio was significantly greater in group 2 than in groups 1 and 3 was was correlated with SBP, DBP and MAP
- At week 24, average blood pressure values in group 1 increased towards those of group 2.

Blood Pressure Values at Eight and 24 Weeks, and Urinary Sodium:creatinine Ratio at Eight Weeks

Variables	Treatment Group 1 (LSMW-Low-Sodium intake)	Treatment Group 2 (HSTW-High-Sodium intake)	Control Group 3 (Breastfed-Lowest Sodium Intake)
Eight weeks			
Systolic blood pressure (mmHg)	85.6±7.9	90.9± 7.7*	83.3±6.5
Diastolic blood pressure (mmHg)	48.9±6.9	60.0± 5.7*	46.5±8.7
Mean arterial pressure (mmHg)	60.7±6.4	69.6± 6.6*	59.1±7.5
Urinary sodium:creatinine ratio	1.2±0.21	2.6± 0.30*	1.1±0.25
24 weeks			
Systolic blood pressure (mmHg)	93.2±6.3	95.1±6.0**	88.3±4.4
Diastolic blood pressure (mmHg)	57.3±6.9	63.2±7.4**	53.8±7.4
Mean arterial pressure (mmHg)	68.9±5.5	71.4±8.6**	63.1±8.2

*P<0.05 compared with groups 1 and 3.

**P<0.05 compared with group 3.

Other Findings

- Heart rate did not differ between study groups during the entire study period
- The urinary excretion of either potassium of calcium did not differ between groups, and there was no correlation between urinary excretion of potassium and calcium and blood pressure.

Author Conclusion:

- This study shows unequivocally that diluted milk formula with tap water containing a high

sodium content will result in the infant being fed a high-salt diet. To achieve equivalence to breast milk, infant formula should be diluted with low-salt water
- Blood pressure in the neonate is increased by a high sodium intake via drinking water
- Less sodium as the norm for infants and children would probably reduce the prevalence of essential hypertension in generations to come.

Reviewer Comments:

Limitations

- *Small sample size (sample size decreased by 24th week presumably due to drop-outs, but authors did not discuss reason for dropouts)*
- *Short duration of intervention (Eight weeks for initial sample and 24 weeks for smaller final sample)*
- *No information provided on dietary intake (i.e., formula intake, solid food intake between week 8 and week 24).*

According to the Authors

The determination of sodium intake by only one urine sample has the potential of being an inaccurate estimate (the authors note that they have previously showed that the urinary sodium:creatinine ratio correlates well with 24-hour sodium measurements.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes

1.3.		Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**		???
2.1.		Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.		Were criteria applied equally to all study groups?	Yes
2.3.		Were health, demographics, and other characteristics of subjects described?	???
2.4.		Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**		???
3.1.		Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.		Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.		Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.		If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.		If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.		If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**		No
4.1.		Were follow-up methods described and the same for all groups?	???
4.2.		Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.		Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.		Were reasons for withdrawals similar across groups?	???
4.5.		If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A

5. **Was blinding used to prevent introduction of bias?** `No`

5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? `No`

5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) `???`

5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? `N/A`

5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status? `N/A`

5.5. In diagnostic study, were test results blinded to patient history and other test results? `N/A`

6. **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** `???`

6.1. In RCT or other intervention trial, were protocols described for all regimens studied? `Yes`

6.2. In observational study, were interventions, study settings, and clinicians/provider described? `N/A`

6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? `Yes`

6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured? `???`

6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described? `No`

6.6. Were extra or unplanned treatments described? `No`

6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? `???`

6.8. In diagnostic study, were details of test administration and replication sufficient? `N/A`

7. **Were outcomes clearly defined and the measurements valid and reliable?** `Yes`

7.1. Were primary and secondary endpoints described and relevant to the question? `Yes`

7.2. Were nutrition measures appropriate to question and outcomes of concern? `Yes`

7.3. Was the period of follow-up long enough for important outcome(s) to occur? `???`

7.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? `Yes`

7.5. Was the measurement of effect at an appropriate level of precision? `Yes`

7.6.	Were other factors accounted for (measured) that could affect outcomes?		???
7.7.	Were the measurements conducted consistently across groups?		Yes

8. Was the statistical analysis appropriate for the study design and type of outcome indicators? — Yes

8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A

9. Are conclusions supported by results with biases and limitations taken into consideration? — Yes

9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes

10. Is bias due to study's funding or sponsorship unlikely? — ???

10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	???